Conclusions: 1) LQTS pts show non-stationary TWA more frequently than stationary TWA. Usually, 30-40 beats out of 128 were alternating. 2) Our correlative method was more effective than SM in non-stationary TWA detection. 3) Non-stationary TWA is associated with higher heart rate.

844 Serum Lipids and Hemostasis: Human Studies

Tuesday, March 31, 1998, 10:30 a.m.–Noon
Georgia World Congress Center, Room 255W

10:30

844-1 Treatment of Hypercholesterolemic Patients With and Without Coronary Disease With Pravastatin Decreases Thrombus Formation Under Dynamic Flow Conditions

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Background: Lowering cholesterol (C) decreases platelet reactivity in coronary disease (CAD) patients, but its effect on non-CAD patients has not been previously described.

Methods: We prospectively studied 40 stable patients with untreated LDL-C >145 mg/dl. CAD patients received Pravastatin (Prav), and non-CAD patients were randomized to Prav vs. Placebo (double-blind). All patients were on AHA step 1 diet. Thrombus formation was assessed blindly with a previously validated ex-vivo perfusion chamber system: non-anticoagulated blood was passed directly from the patient's vein over a standard substrate (porcine aortic media), under controlled rheologic conditions mimicking mild arterial stenosis (shear rate 1690s^{-1}). Perfusions were performed at baseline, 3, and 6 months. Specimens were stained with CME, and for fibrinogen. The cross-sectional thrombus area (TA, in $\mu m^2 \times 10^3$) was planimetered.

Results: Both Prav groups showed decreased LDL-C by 30% within 6 weeks (188 to 126 mg/dl, p < 0.001 vs baseline), and decreased TA (table). Placebo produced no changes in either LDL-C or TA. ΔLDL-C and ΔTA were modestly correlated (r = 0.49; p < 0.005).

	Baseline TA	3 month TA	6 month TA
Prav. +CAD (n = 16)	12.5 ± 2.1	10.9 ± 2.9*	10.5 ± 3.8**
Prav. −CAD (n = 12)	14.6 ± 3.4	11.6 ± 2.3**	10.4 ± 2.8**
Placebo, −CAD (n = 12)	12.2 ± 1.9	12.8 ± 2.7	13.2 ± 4.5

* p < 0.07, ** p < 0.04 vs. baseline. Values as mean ± SD

Conclusion: Prav therapy significantly decreased ex-vivo thrombus formation in high LDL-C patients, with and without CAD. This may, in part, explain the beneficial effects of Prav in primary as well as secondary prevention of CAD.

10:45

844-2 Lipid Lowering Therapy Reduces Blood Thrombogenicity in Hypercholesterolemic Patients: Effect of Simvastatin

U. Rauch, J.J. Badimon, D.A. Vorchheimer, I. Guzman, K. Harris, P. Harris, D.A. Sandler, J.T. Fallon, V. Fuster, J.H. Chesebro. *Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY, USA*

Lipid reduction improves clinical outcome of CAD patients despite minor angiographic plaque regression. Normalization of endothelial function and plaque stabilization are two of the proposed mechanisms. We hypothesize that lipid reduction modulates blood thrombogenicity. Blood thrombogenicity was measured as thrombus formation (THR) in an ex vivo perfusion chamber. Hyperlipidemic patients (10 with and 5 without CAD) with total cholesterol (Cho) >220 mg/dl and LDL >140 mg/dl at baseline and after 3- months treatment with simvastatin (20 mg/day) were studied. Blood was perfused directly from the patient into the chamber at shear conditions typical of a mild coronary stenosis (1690/s) for 5 minute periods. Porcine aortic tunica media (model of severe arterial injury) served as the thrombogenic substrate. Thrombus formation was measured as area (μm^2/mm), analyzed by 2 independent blinded observers using computer-assisted planimetry.

Patients	baseline			3-months		
	Cho	LDL	Thrombus	Cho	LDL	Thrombus
CAD	253	189	10482	167*	106*	8605*
No-CAD	277	205	9988	183*	110*	7891*
All Pts	261	172	10317	194*	108*	8366*

* p < 0.05

Lipid reduction by simvastatin reduces blood thrombogenicity. It was previously suggested that this effect is exclusive to pravastatin. Our results indicate that the antithrombotic effect is mediated by lipid reduction and independent of the hypolipidemic agent used.

11:00

844-3 Elevation of Plasminogen Activator Inhibitor Type-1 (PAI-1) in Normal Subjects by Induction of Hyperinsulinemia With Hyperglycemia and Hypertriglyceridemia

J. Calles-Escandon, S. Mirza, B.E. Sobel, D.J. Schneider. *University of Vermont, Burlington, VT, USA*

Hypofibrinolysis caused by increased PAI-1 has been implicated in the vasculopathy of type 2 diabetes, typified by increased insulin, glucose and triglycerides. However, short term infusions of insulin have not increased PAI-1 in normal subjects. We hypothesized that induction of increased insulin accompanied by increased glucose and triglycerides would increase PAI-1. Accordingly 30% glucose and 10% Intralipid were infused for 6 hours in 10 normal lean individuals (54 ± 3 y) resulting in increased insulin (42 ± 5 μU/dL), glucose (200 ± 24 mg/dl) and triglycerides (425 ± 45 mg/dl) simulating changes in type 2 diabetes.

Results: In contrast to results with infusion of saline alone (n = 16) and euglycemic hyperinsulinemic clamps (n = 10, serum insulin = 89 ± 7 μU/dL), PAI-1 in blood increased significantly 6 hr after the onset of infusion (15 ± 5 ng/ml, p < 0.05 vs baseline = 7.4 ± 1.1, saline 6 hr = 3.4 ± 1.1 and insulin at 6 hr = 3.7 ± 0.8) and remained elevated for an additional 6 hr (combined infusion = 13.8 ± 3.8 ng/ml, saline = 6.7 ± 2 ng/ml, insulin alone = 7.8 ± 1.7 ng/ml, p = 0.06).

Conclusions: Our data suggest that combined hyperinsulinemia, hypertriglyceridemia and hyperglycemia are likely to contribute to hypofibrinolysis of type 2 diabetes by increasing the blood levels of PAI-1. Moreover, these results underscore the potential importance of modifying insulin resistance as well as achieving glycemic and lipidemic control in individuals with type 2 diabetes.

11:15

844-4 Beneficial Effect of Estrogen Therapy on Fibrinolysis Is Independent of Changes in Low-Density Lipoprotein Levels

K.K. Koh, M.N. Bui, L. Hathaway, R.O. Cannon III. *NHLBI, NIH, Bethesda, MD, USA*

We have previously shown that oral conjugated equine estrogen (CEE) reduces plasminogen activator inhibitor (PAI-1) levels in postmenopausal women, an effect associated with proportionate increases in degradation products of fibrin. However, oral estrogen reduces low-density lipoprotein cholesterol (LDL-C) levels that may account for PAI-1 effects, as oxidized LDL stimulates endothelial synthesis of PAI-1 in cell culture experiments. To assess the importance of LDL on PAI-1, we administered CEE 0.625 mg, simvastatin 10 mg, or the combination daily for 6 weeks each to 25 hypercholesterolemic (LDL = 165 ± 37 mg/dL; mean ± SD) postmenopausal women in a randomized, double-blind, double-crossover study. Data = % change from respective pretreatment values.

	CEE	Simvastatin	CEE/Simvastatin
LDL-C	-1* ± 11*	-24 ± 14**	-33 ± 13**
ApoB	-8 ± 8*	-23 ± 10**	-28 ± 11**
PAI-1	22 ± 47**	+27 ± 85	-23 ± 42***

*P < 0.001, **P < 0.005, ***P < 0.02 vs. respective pretreatment baseline values. † P < 0.005 vs. CEE

Only therapy including CEE reduced PAI-1 antigen levels, despite a greater effect of simvastatin on reduction in LDL-C and apolipoprotein B levels. Further, there was no synergism of combined CEE and simvastatin therapy on PAI-1 levels. These data suggest that estrogen reduces PAI-1 levels independent of changes in LDL. This primary effect of CEE on fibrinolytic potential may favor its use in hypercholesterolemic postmenopausal women, even if they are already on lipid-lowering therapy.

11:30

844-5 Low-Dose Estrogen Improves Serum Lipids, Homocysteine, and Fibrinolysis Without Altering Markers of Hemostasis in Elderly Men

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The effect of estrogen on cardiovascular risk factors in men is not well defined.